Alerts, Notices, and Case Reports

Combination Therapy With an Angiotensin Converting Enzyme Inhibitor and an Angiotensin-II Receptor Antagonist for Refractory Essential Hypertension

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THE TREATMENT OF severe essential hypertension can be a difficult clinical challenge. Despite the wide range of pharmacological options, some patients have poor blood pressure control even with multidrug therapy. It is well-established that increased circulating or tissue angiotensin II activity can be a major cause of hypertension.[1] Angiotensin converting enzyme (ACE) inhibitors have shown to be effective in the treatment of severe hypertension and are frequently used for this purpose.[2–4] However, even with the combination of high doses of ACE inhibitors (enough to effectively block ACE activity), diuretics, and adrenergic antagonists, some patients continue to exhibit high blood pressure.

ACE inhibitors are attractive for the treatment of hypertension because they effectively block the production of angiotensin II while simultaneously decreasing ACE-mediated degradation of bradykinin, a potent vasodilator. Alternative pathways for the production of angiotensin II, which do not involve ACE, have been described.[5–7] We considered the possibility that in patients whose pressures are resistant to high doses of ACE inhibitors, angiotensin II activity in the systemic resistance vessels might not be completely suppressed by ACE inhibitors. An alternative way of preventing the effects of angiotensin II is to block the receptor through which angiotensin II exerts its effects. If high doses of an ACE inhibitor do not result in an adequate antihypertensive response, further prevention of angiotensin II effects theoretically can be attained with the addition of an angiotensin II–receptor blocker. Such a combination would allow ACE inhibitor-induced bradykinin augmentation but reduce angiotensin II production and block effects of angiotensin II produced by non-ACE pathways. We postulated that combining the two drug types would likely exceed the effect of either drug used alone.

We describe four patients with severe hypertension, refractory to other regimens, who were successfully treated with the combination of an ACE inhibitor and an angiotensin II–receptor antagonist. Each of these patients failed to respond adequately to high doses of an ACE inhibitor combined with other classes of antihypertensive agents; each experienced considerably better pressure control, however, when an angiotensin II–receptor antagonist was added. This finding is compatible with the hypothesis that in some hypertensive patients substantial angiotensin II is produced by non-ACE mechanisms and that employing a dual approach to preventing Renin-angiotensin system effects may be useful in treating these individuals.

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Reports Of Cases

Patient 1

A 73-year-old man, weighing 168 pounds, had a long history of severe essential hypertension. The patient was on an antihypertensive regimen consisting of an ACE inhibitor, quinapril (40 mg a day); hydrochlorothiazide (25 mg a day); labetalol (200 mg twice a day); and clonidine (0.2 mg twice a day). He continued to note morning systolic blood pressures of 182 to 226 mm of mercury and diastolic blood pressures of 70 to 80 mm of mercury. He had previously been treated with long-acting nifedipine, which was ineffective, and beta adrenergic blockers, which were poorly tolerated and resulted in bradycardia and fatigue. There was considerable fluctuation in his response to labetalol.

The results of his echocardiogram showed left ventricular hypertrophy. Serum potassium and creatinine levels were normal. Because of symptomatic bradycardia (with pulse rates as low as 46 beats per minute), it became necessary to reduce the dosage of labetalol to 100 mg two times a day, and an AT1 antagonist, losartan (50 mg two times a day), was added to his regimen. Over the next three months, systolic pressures were 172 to 178 mm of mercury, and diastolic pressures were 68 to 80 mm of mercury; excessive bradycardia was no longer present (his heart rate was 60 beats per minute).

Patient 2

An 86-year-old man, weighing 187 pounds, who had a long history of severe essential hypertension did not attain sufficient blood pressure control on a regimen consisting of quinapril (40 mg a day), hydrochlorothiazide (25 mg a

day), and atenolol (50 mg a day). His systolic blood pressures on this regimen were 176 to 186 mm of mercury, and his diastolic pressures were 106 to 108 mm of mercury. He had experienced an episode of confusion thought to be related to his high pressures. Treatment with atenolol resulted in an rise in his PR interval on his electrocardiogram. Serum potassium and creatinine levels were normal. After several months of poor control, losartan (initially 50 mg a day and subsequently 100 mg a day) was added to his regimen, and the dose of atenolol was lowered to 25 mg a day because of his increased PR interval. These changes led to excellent control of his blood pressure, with his latest reading at 136/64 mm of mercury. The patient continues to do well on this regimen.

Patient 3

A 62-year-old woman, weighing 187 pounds, had a history of an inferior wall myocardial infarction and several years of poorly controlled hypertension. She was intolerant of therapy with beta adrenergic blockade and diltiazem, a calcium blocker, and was hospitalized for an episode of congestive heart failure. Subsequent therapy with enalapril (20 mg twice a day) and furosemide (40 mg a day) relieved her symptoms of heart failure, but she continued to have elevated blood pressures of approximately 170/104 mm of mercury. Results of her echocardiogram revealed normal systolic and diastolic function as well as normal wall thickness. Serum creatinine and potassium levels were normal. Adding losartan (50 mg twice a day) to her medical regimen has resulted in systolic pressures of 130 to 142 mm of mercury, with diastolic pressures in the 80s. The patient is asymptomatic on this medical regimen and has had no further episodes of congestive heart failure.

Patient 4

A 72-year-old man, weighing 260 pounds, had a long history of hypertension that had been resistant to a variety of medical therapy combinations. On quinapril (40 mg twice a day), doxazosin (8 mg a day), and furosemide (40 mg a day), he presented with a blood pressure of 197/85 mm of mercury and mild heart failure, including dyspnea and pulmonary congestion. His electrocardiogram showed left ventricular hypertrophy with strain. His echocardiogram revealed concentric left ventricular hypertrophy with normal systolic function and moderate left ventricular dilatation. Serum potassium and creatinine levels were normal. The addition of losartan (100 mg twice a day) to his medical regimen resulted in a reduction of his systolic and diastolic blood pressures—to 160 to 168 and 70 to 78 mm of mercury, respectively. The patient's dyspnea and pulmonary congestion disappeared.

Discussion

The classic pathway of angiotensin II synthesis is catalyzed by the ACE, which is present in plasma and various other tissues.[1] There have been several reports, however, of angiotensin II synthesis by pathways, involving chymase or other enzymes, that do not require ACE.[5,6] Conclusions of studies involving myocardial angiotensin II production in patients with heart failure have covered the spectrum, with one report stating that non-ACE pathways are extremely important in the process,[5] and another report concluding that all or nearly all angiotensin II production is prevented with ACE inhibition.[8] The effectiveness of ACE inhibitors in lowering the blood pressures of essential hypertensive patients does not exclude the possibility that in some patients the non-ACE pathway of angiotensin II production could be an important modulator of blood pressure. In support of this thesis, a recent study of spontaneously hypertensive rats concluded that the combination of an ACE inhibitor and an angiotensin II inhibitor reduced blood pressure more than either agent alone.[9]

All four of the patients in this report were initially on doses of ACE inhibitors that are generally considered to provide complete blockade of ACE.[2–4] In all four patients, the addition of the AT1 blocker losartan to an ACE inhibitor markedly improved blood pressure control. There are two likely explanations for the success of adding losartan to the previous regimens: either the ACE inhibition was incomplete or there were substantial amounts of angiotensin II produced by non-ACE pathways.

Prolonged use of ACE inhibitors can result in an up to two-fold rise in angiotensin I activity and a shorter duration of angiotensin II suppression.[10] This can lead to decreased efficacy of ACE inhibitors in the treatment of hypertension. The doses of ACE inhibitors in our four patients were so high that they normally would be expected to prevent all meaningful ACE activity.[2–4]

The alternative explanation is that there was substantial production of angiotensin II by non-ACE pathways in these patients. A previous study investigated the relative effects of ACE inhibitor therapy, angiotensin II antagonist therapy, and combination therapy on blood pressure in sodium-depleted subjects.[11] In these subjects, combination therapy induced a greater decrease in mean blood pressure than observed with each agent alone. In a recent study of spontaneously hypertensive rats, a similar benefit using the combination of an ACE inhibitor and an AT1 blocker was noted.[9]

Regardless of the underlying mechanism, the combination of an ACE inhibitor and an AT1 receptor blocker allowed us to bring blood pressure under reasonable control in four patients whose hypertension was highly refractory to combinations of an ACE inhibitor with other drugs. Use of an ACE inhibitor permits the antihypertensive effect of increased bradykinin production to occur, an effect that is not seen with angiotensin-II receptor blockade alone.

Conclusion

Combination therapy with an ACE inhibitor and an angiotensin-II receptor blocking agent has a role in the treatment of severe, refractory essential hypertension.

Although the long-term efficacy and mortality benefit of this therapy has not been described, one would expect it to parallel that of other antihypertensive regimens. This type of combination therapy is likely to provide the benefits—including the prevention of left ventricular hypertrophy and improvement of proteinuria and heart failure—that are associated with ACE inhibitors alone.

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Glibenclamide-Induced Cholestasis

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GLIBENCLAMIDE IS A potent, long-acting second-generation sulphonylurea that is probably the most widely used oral hypoglycemic agent in the world. The drug is safer than first-generation oral hypoglycemic agents. Although not frequently reported in the American population,[1,2] (a search on Medline's website revealed fewer than fifteen reported cases) cholestatic liver disease remains a major side effect[3] that is independent of the duration of therapy. We report a case of reversible cholestasis induced by glibenclamide.

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A 64-year-old man with a twenty-year history of type 2 diabetes mellitus presented to the hospital on April 23, 1996. He had been treated with glibenclamide 10 mg per day for at least the last four years and had a six- to eight-week history of fatigue, nausea, and malaise, complicated by a one-week history of jaundice, sporadic episodes of vomiting, dark urine, and pale stools. He reported weight loss of approximately five pounds. There was no history of fever, abdominal pain, skin rash, pruritus, or arthralgia, nor any history of alcohol abuse, previous liver disease, blood transfusion, exposure to toxins, or additional recent drug intake.

The patient's physical examination revealed marked icterus and hepatomegaly. Results of a hemogram were normal, as were his eosinophil count, coagulation studies, serum amylase level, renal function test, and erythrocyte sedimentation rate. His glycemic control had been erratic for approximately one month before presentation. The patient's initial liver chemistry panel and subsequent results are depicted in Table 1. His serum albumin level was 2.9 grams per dl. Serological tests for Hepatitis A, B, and C viruses, *Helicobacter pylori*, antimitochondrial antibody, and antinuclear antibody were all negative. Abdominal ultrasonography and CT scan of the abdomen did not reveal significant abnormalities. Two endoscopic retrograde cholangiopancreatograms (ERCPs)—performed on April 23 and May 3—did not show evidence of extrahepatic obstruction. The patient's serum total bilirubin level increased from 9.4 mg per dl on April 23 to 19.8 mg per dl on May 8, despite his normal ERCP (Figure 1).

A liver biopsy specimen examined at Mayo Clinic (Rochester, MN) showed portal and periportal inflammation and edema with a few scattered poorly defined granulomas, proliferation of ducts, focal ductopenia, neutrophil infiltration of the portal areas, and prominent centrilobular hepatocanalicular cholestasis (Figure 2). There was no evidence of viral inclusion bodies or fatty change in the biopsy specimen. Glibenclamide was discontinued on May 8, and the patient was started on insulin therapy. After eight weeks, the laboratory variables had become essentially normal. Six months later, the patient was asymptomatic and had no clinical or biochemical evidence of liver disease (Table 1). A rechallenge test with glibenclamide was not conducted for ethical reasons.

The differential diagnosis considered in this case included choledocholithiasis, primary biliary cirrhosis, and hepatitis. It is important to note, however, that the time-course of events, the patient's normal abdominal ultrasound, and ERCPs with no evidence of biliary ductal dilation argue strongly against a diagnosis of choledo-